This paper is available online at www.jbc.org
THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 284, NO. 12, p. 7405, March 20, 2009

Unstable Nucleotide Repeat Minireview Series: A Molecular Biography of Unstable Repeat Disorders*

Published, JBC Papers in Press, October 28, 2008, DOI 10.1074/jbc.R800067200

Harry T. Orr[1]

From the Institute of Human Genetics and the Departments of Biochemistry, Biophysics, and Molecular Biology and of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota 55455

Expansion of an unstable nucleotide repeat is a mutational mechanism that is apparently unique to humans and is known to cause a variety of neurological disorders. This collection of minireviews examines several of these unstable repeats, focusing on those where there is considerable molecular information on how the mutation alters function.

Until the discovery of unstable trinucleotide repeats as a cause neurological disorders (1), it was thought that disease-causing mutations are stably transmitted from parent to offspring. Expansion of unstable repeats causes a variety of inherited neurological disorders ranging from developmental childhood forms of X-linked mental retardation to the typically late-onset neurodegenerative disorders such as Huntington disease, many of the inherited ataxias, and the muscular dystrophies (Fig. 1). Discovery of these dynamic mutations, a mutational mechanism that appears to be restricted to the human genome, provides a molecular explanation for the variability in expressivity or severity of the disease phenotype: the larger the expansion, the earlier the onset and the more severe the disease course. As a group, these disorders provide a fertile area of investigation for those interested in basic molecular processes that span the range from DNA repair, replication, and transcription and RNA processing to protein dysfunction and cellular homeostasis.

The first three minireviews of this series explore molecular aspects of repeats that are transcribed but not translated. The minireview entitled "Mutation Spectra in Fragile X Syndrome Induced by Deletions of CGG·CCG Repeats" by Robert D. Wells (Texas A&M Health Science Center) discusses how the fragile X syndrome repeats mediate deletion mutations. This minireview shows how studies in bacteria contribute to the molecular understanding of this mutational mechanism. In the article by Daman Kumari and Karen Usdin (National Institutes of Health), the ability of the repeats at the fragile X syndrome locus and the FRAXE mental retardation and FRA12 mental retardation loci to promote the formation of heterochromatin, thereby silencing gene expression, is examined. Both RNA- and DNA-based mechanisms are discussed. Jason R. O'Rourke and Maurice S. Swanson (University of Florida) go on to review the RNA-based gain-of-function mechanisms thought to underlie pathogenesis for the three disorders myotonic dystrophy, fragile X tremor ataxia syndrome, and spinocerebellar ataxia type 8. These authors explore the means by which RNA with an expanded repeat can disrupt alternative splicing of mRNAs through an interaction with key regulators of alternative splicing. They also discuss how antisense transcription might contribute to pathogenesis.

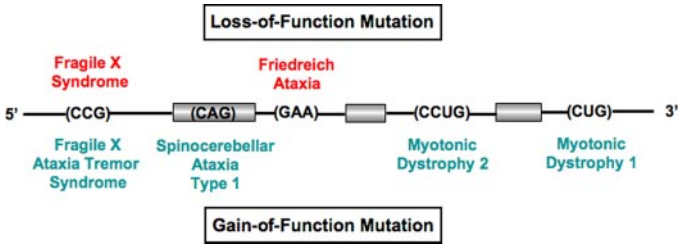

FIGURE 1. **Unstable nucleotide repeats and their associated neurological disorders.** The sequences and locations of five unstable nucleotide repeats in which expansion leads to a neurological disorder are indicated within a stylized gene. Disorders caused by a loss-of-function mechanism are indicated above the gene in *red*, and those resulting from a gain-of-function mechanism are indicated below in *green*.

The final two minireviews in this series discuss the polyglutamine-based disorders. Here, the repeat is not only transcribed but also translated into protein encoding a stretch of glutamines. In these disorders, the evidence strongly supports the idea that pathogenesis is due to a gain of function residing in the mutant polyglutamine protein. Huda Y. Zoghbi (Baylor College of Medicine) and I focus our discussion on the disease spinocerebellar ataxia type 1, in which expansion of a glutamine in the ataxin-1 protein causes disease. A critical aspect of this work is that it illustrates the importance of studying the normal biochemistry of the full-length protein to understand the pathogenesis. In the final contribution to the series, J. Lawrence Marsh, Tamas Lukacsovich, and Leslie Michels Thompson (University of California, Irvine) describe the modeling of several polyglutamine disorders in variety of organisms, including nonmammalian species such as yeast, worms, flies, mice, and non-human primates. They discuss the use of these models in the elucidation of molecular pathways as targets for therapeutic development.

REFERENCE

1. Orr, H. T., and Zoghbi, H. Y. (2007) *Annu. Rev. Neurosci.* **30,** 575–621

* This minireview will be reprinted in the 2009 Minireview Compendium, which will be available in January, 2010.

[1] To whom correspondence should be addressed. E-mail: orrxx002@umn.edu.